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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,530	11/28/2000	Clay B. Siegal	9632-012	7001

20583 7590 06/04/2003

PENNIE AND EDMONDS  
1155 AVENUE OF THE AMERICAS  
NEW YORK, NY 100362711

EXAMINER
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CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 06/04/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.  
09/724,530

Applicant(s)  
Siegall et al

Examiner  
Karen Canella

Art Unit  
1642



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 months MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_\_
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 26, 27, 32, 33, and 37-114 is/are pending in the application.
- 4a) Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 26, 27, 32, 33, and 37-114 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some\* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_ 6) ☐ Other:

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### **DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 22, 2002 has been entered.
2. Claims 26, 27 and 37 have been amended. Claims 58-114 have been added. Claims 26, 27, 32, 33 and 37-114 are pending and under consideration.
3. Claims 67, 69-74 and 81 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot serve as a basis for other multiple dependent claims. See MPEP § 608.01(n). Accordingly, claims 67, 69-74 and 81 have not been further treated on the merits.
4. Claims 60, 61, 62, 68, 75-80, and 82, 86-89, 95, 98, 101, 104, 107, 110 and 113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 60 and 61 are rendered vague and indefinite by reference to a trade name, the object of which can be variable.
5. Claims 26, 27, 32, 33 and 37, 41-48, 50-55, 57-65, 68, 75-77 and 82-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Melief et al (U.S. Application 2003/0022860, priority to May 23, 1998) and the abstract of Schultze et al (Blood, 1996, vol. 88, No. 10, suppl. 1, part 1-2, page 162A) and the abstract of Sotomayor et al (Blood, 1998, vol. 92, No. 10, suppl.

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1, part 1-2, page 541A) and Schultze (Haematology and Blood Transfusion, 1998, Vol. 39, pp. 716-731) and Costello et al (Archivum Immunologiae et Therapiae Experimentalis, Feb 1999, vol. 47, pp. 83-88) and Buhmann et al (Blood, 1999, Vol. 93, pp.1992-2002) and Caux et al (journal of Experimental Medicine, 1994, vol. 180, pp. 1263-1272) and Cella et al (Journal of Experimental Medicine, 1996, Vol. 184, pp. 747-752) all in view of de Boer (U.S. 5,874,082) and Schlom (In: Molecular foundations of Oncology, Sameule Broader, Ed, 1991, pages 95-134) .. The instant claims are drawn to methods of treating cancer comprising administering chimeric or humanized antibodies which bind to CD40 and increase the binding of CD40L to CD40 by at least 45%. The specification teaches on page 5, lines 10-14 that said chimeric or humanized antibodies are constructed based on the variable chain and CDR regions of the S2C6 antibody.

Melief et al teach a method to treat cancer by up regulating the immune response to tumor antigens comprising administering CD40 binding molecules together with CTL activating peptides. Melief et al teach that the CD40 binding molecules can include antibody molecules and immunoglobulin fragments such as Fab, (Fab')<sub>2</sub> and Fv [0008]. Melief et al further teach that T-cell help for CTL priming is mediated through CD40-CD40 ligand interactions and lack of CTL priming can be restored by monoclonal antibody activation of bone-marrow derived antigen presenting cells in the presence of CTL activating peptides, such as tumor antigens[0010] and that the administration of the anti-CD40 antibody in combination with said tumor antigens is a means for converting tolerization to strong CTL activation[0011]. Melief et al do not specifically teach a method of treating cancer comprising administration of a humanized or chimeric version of the S2C6 antibody in combination with CD40 ligand.

The abstract of Schultze et al teaches that human CD40 activated B-cell have advantages over dendritic cells for presentation of tumor antigens. The abstract teaches that human B cells activated by CD40 cross linking are highly efficient antigen-presenting cells to present tumor peptides and that said activated B cells induced a higher level of T cell proliferative response in vitro, and additionally, CD40 activated B-cells remain fully functional even in the presence of

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immunosuppressive cytokines such as Il-10 and TGF-beta. The abstract of Schultze et al does not teach a method of treating cancer comprising administration of a humanized or chimeric version of the S2C6 antibody in combination with CD40 ligand.

The abstract of Sotomayor et al teaches that in vivo ligation of CD40 prevents the induction of tumor-antigen-specific t-cell tolerance. The abstract teaches that CD4 T-cells specific for a tumor antigen become tolerant early in the course of tumor progression and that this has been demonstrated in B cell lymphoma and renal cell carcinoma. Sotomayor et al teaches in experiments with mice challenged with transplanted renal carcinoma cells, CD4 T cells specific for an antigen on the renal carcinoma were tolerized in mice not receiving an anti-CD40 antibody. The abstract teaches administration of the anti-CD40 antibody and the CD40 ligand by means of the T cell, but does not teach the administration of a humanized or chimeric version of the S2C6 antibody in combination with CD40 ligand.

Costello et al teach that B cells from chronic Lymphocytic Leukemia inhibit the immune response by the suppression of the CD40 triggered T lymphocyte stimulation (page 85, second column, lines 35-38) Costello et al further teach that cancer cell stimulation by CD40 was shown to be highly efficient in the restoration of immune response against weakly immunogenic tumors such as follicular lymphoma cells, and that once T lymphocytes have been primed by the tumor cells stimulated with CD40 they are capable of efficient recognition and destruction of cells from the same lymphoma even not stimulated by CD40 (page 86, first column, lines 9-23 of the first full paragraph). Costello et al do not teach the administration of a humanized or chimeric version of the S2C6 antibody in combination with CD40 ligand.

Schultze teaches a method of treating follicular lymphoma comprising administering CD40 activated follicular lymphoma vaccine. (Page 728-729, under the heading "Translation of the Results into the clinic: Vaccination with CD40 activated follicular Lymphoma Cells"). Schultze teaches that autologous TIL cells taken from follicular lymphoma patients can be stimulated with CD40 activated follicular lymphoma cells to lyse said lymphoma cells whereas normal B-cell were

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not lysed by the TIL in vitro (page 724, under the heading "Repair of the Defects in T-TIL", figure 6A-E, and page 726, first column, lines 10-17). Schultze summarizes his teachings as CD40 activated follicular lymphoma cells can function as antigen presenting cells and can prime T-cell tumor infiltrating lymphocytes to recognize and kill the primary follicular lymphoma cells in vitro (page 7272, second column, first full paragraph). Schultze et al corroborates the evidence set forth in the abstract of Schultze et al (1996) above, in that the presence of Il-10 and or TGF-beta did not decrease T cell proliferation induced by CD40 activated follicular lymphoma cells, suggesting that only CD40 activated follicular lymphoma cells were capable of overcoming t-cell unresponsiveness induced by said cytokines (pages 727 to 728 bridging sentence). Schultze does not teach the administration of a humanized or chimeric version of the S2C6 antibody in combination with CD40 ligand.

Buhmann et al teach that CD40 stimulated chronic lymphocytic leukemia cells provide a proliferative stimulus to T-cells, and that said stimulated lymphocytic leukemia cells activated autologous CD4 T-cells to exhibit a Th1-type cytokine pattern (page 1996-1999, under the headings "CD40-CLL cells induce a proliferative T-cell response" and "Different effector cells are induced by subsequent stimulation of allogenic versus autologous T cells with CD40-CLL cells"). Buhmann et al teach that although a CD8 T-cell proliferative response was not triggered by the CD40-CLL cells the resultant CD4 Th1 cells activated by the CD40 stimulated CLL cells were able to eliminate CLL cells in vitro through a Fas-dependent apoptotic pathway (page 2000, second column, third full paragraph). Buhmann et al do not teach the administration of a humanized or chimeric version of the S2C6 antibody in combination with CD40 ligand.

Caux et al teach that CD40 triggering of dendritic Langerhans cells enhances cell survival, maintains or increases high levels of accessory molecules and produces cytokines. Caux et al teach that induction and maintenance of high levels of said accessory molecules results in a strong T-cell activation, and that the most dramatically unregulated molecule is B7-2 which plays a predominant role in dendritic cell dependent T cell activation (page 1270, first column, lines 1-25

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under the heading "Discussion"). Caux et al do not teach the administration of a humanized or chimeric version of the S2C6 antibody in combination with CD40 ligand.

Cella et al teach that the CD40 ligation on dendritic cells increases T-cell stimulatory capacity of dendritic cells and favors the TH1 response (pages 749-750, under the heading "CD40 Ligation on Dcs Results in Upregulation of adhesion and costimulatory molecules and in Enhanced T Cell Stimulatory Capacity"). Cella et al do not teach the administration of a humanized or chimeric version of the S2C6 antibody in combination with CD40 ligand.

deBoer teaches methods for treating antibody mediated diseases comprising the administration of antagonist humanized monoclonal antibodies which bind to CD40. DeBoer teaches that the prior art antibodies which bind to CD40 have a stimulatory effect on B-cells and have been shown to mimic the effect of T-helper cells in B-cell activation (column 2, lines 45-59). DeBoer teaches that the "old" S2C6 antibody can co-stimulate anti-IgM B-cell proliferation ((column 4, lines 38-50 and figure 5A). DeBoer teaches the humanization of the 5D12, 3C6, and 3A8 antibodies by virtue of said antibodies being capable of inhibiting the B-cell response and the use of said antibodies in the treatment of antibody-mediated disease (column 2, lines 62-67). DeBoer does not teach the humanization of the S2C6 antibody.

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of murine antibodies only the first and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the murine antibodies (pages 97-98, bridging paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to humanize the S2C6 antibody and use said humanized antibody in a method of inducing an immune response to a tumor antigen comprising administering said antibody. Further it would be obvious that an autologous T-cell specific for a tumor antigen and

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activated ex- vivo by can also be administered with said antibody, wherein the autologous T-cell inherently comprises CD40 ligand.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of

1. Melief et al on a method to treat cancer by up regulating the immune response to tumor antigens comprising administering CD40 binding molecules together with CTL activating peptide and that T-cell help for CTL priming is mediated through CD40-CD40 LIGAND interactions.

2. Schultze or the abstract of Schultze et al on the advantages of human CD40 activated B-cell have advantages over dendritic cells for presentation of tumor antigens, wherein said activated B cells induced a higher level of T cell proliferative response in vitro, and additionally, CD40 activated B-cells remain fully functional even in the presence of immunosuppressive cytokines such as Il-10 and TGF-beta.

3. The abstract of Sotomayor et al on the prevention of tumor-antigen specific T-cell tolerance in vivo by the ligation of CD40 and the administration of the anti-CD40 antibody and a CD40 ligand wherein the CD40 ligand is comprised by a T-cell.

4. Costello et al on the induction of immune responses against weakly immunogenic cancer antigens by stimulation of CD40 and the production of T lymphocytes that have been primed by the tumor cells stimulated with CD40 which efficiently recognize and destroy cells from the same lymphoma, wherein said lymphoma cells were not stimulated by CD40;

5. Buhmann et al teach on the stimulation of autologous T-cells to produce a Th1 cytokine pattern in response to stimulation by CD40 stimulated chronic lymphocytic leukemia cells, and the induction of apoptosis in chronic leukemia cells resulting from contact with said Th1 CD4 helper T cells.

6. Caux et al on the elevation of B7-2 in dendritic cells after CD40 activation, wherein said upregulation is known to result in strong T-cell activation.



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7. Cella et al on the increases in stimulatory capacity afforded by CD40 ligation on dendritic and the resulting CD4 TH1 response.

8. DeBoer on the capacity of S2C6 to stimulate B-lymphocytes, the humanization of anti-CD40 antibodies and the teachings of Schlom on the necessity of using humanized antibodies versus murine antibodies in human clinical therapies.

One of skill in the art would be motivated to pick the S2C6 for humanization as it exhibits a very strong activation of B-cells after binding to CD40 on said B-cells. One of skill in the art would be motivated to administer the resultant humanized antibody in vivo to activate both B cells and dendritic cells, and to stimulate the Th1 response which would be expected to kill the target tumor cells by means of Fas-dependent apoptosis.

It is noted that none of the references teaches that binding of the S2C6 antibody or the humanized version thereof results in the increase in CD40 ligand binding to the CD40 receptor by at least 45%. However, this would be an inherent property of the claimed humanized and chimeric antibodies derived from S2C6.

6. Claims 26, 27, 32, 33 and 37, 41-65, 68, 75-78 and 82-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Melief et al (U.S. Application 2003/0022860, priority to May 23, 1998) and the abstract of Schultze et al (Blood, 1996, vol. 88, No. 10, suppl. 1, part 1-2, page 162A) and the abstract of Sotomayor et al (Blood, 1998, vol. 92, No. 10, suppl. 1, part 1-2, page 541A) and Schultze (Haematology and Blood Transfusion, 1998, Vol. 39, pp. 716-731) and Costello et al (Archivum Immunologiae et Therapiae Experimentalis, Feb 1999, vol. 47, pp. 83-88) and Buhmann et al (Blood, 1999, Vol. 93, pp.1992-2002) and Caux et al (Journal of Experimental Medicine, 1994, vol. 180, pp. 1263-1272) and Cella et al (Journal of Experimental Medicine, 1996, Vol. 184, pp. 747-752) and de Boer (U.S. 5,874,082) and Schlom (In: Molecular foundations of Oncology, Sameule Broader, Ed, 1991, pages 95-134) as applied to claims 26, 27, 32, 33 and 37, 41-48, 50-55, 57-65, 68, 75-77 and 82-114 above, and further in view of the

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abstract of Bender et al (Human antibodies and Hybridomas, 1993, Vol. 4, pp. 74-79). Claims 49, 56 and 78 specify that the antibodies which bind to CD40 are human antibodies.

The combination of Melief et al (U.S. Application 2003/0022860, priority to May 23, 1998) and the abstract of Schultze et al (Blood, 1996, vol. 88, No. 10, suppl. 1, part 1-2, page 162A) and the abstract of Sotomayor et al (Blood, 1998, vol. 92, No. 10, suppl. 1, part 1-2, page 541A) and Schultze (Haematology and Blood Transfusion, 1998, Vol. 39, pp. 716-731) and Costello et al (Archivum Immunologiae et Therapiae Experimentalis, Feb 1999, vol. 47, pp. 83-88) and Buhmann et al (Blood, 1999, Vol. 93, pp.1992-2002) and Caux et al (journal of Experimental Medicine, 1994, vol. 180, pp. 1263-1272) and Cella et al (Journal of Experimental Medicine, 1996, Vol. 184, pp. 747-752) all in view of de Boer (U.S. 5,874,082) and Schlom (In: Molecular foundations of Oncology, Sameule Broader, Ed, 1991, pages 95-134) render obvious claims 26, 27, 32, 33 and 37, 41-48, 50-55. 57-65, 68, 75-77 and 82-114 with regard to a humanized S2C6 antibody or a single chain fragment thereof. The aforesaid references do not teach a human antibody which binds to CD40.

The abstract of Bender et al teaches that recombinant human antibodies comprising a human Fc fragment can be expressed in mamamlian cell culture by linking Fab fragments screened from combinatorial phage display libraries to human constant regions.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the humanized S2C6 antibodies rendered obvious by the combination of Melief et al (U.S. Application 2003/0022860, priority to May 23, 1998) and the abstract of Schultze et al (Blood, 1996, vol. 88, No. 10, suppl. 1, part 1-2, page 162A) and the abstract of Sotomayor et al (Blood, 1998, vol. 92, No. 10, suppl. 1, part 1-2, page 541A) and Schultze (Haematology and Blood Transfusion, 1998, Vol. 39, pp. 716-731) and Costello et al (Archivum Immunologiae et Therapiae Experimentalis, Feb 1999, vol. 47, pp. 83-88) and Buhmann et al (Blood, 1999, Vol. 93, pp.1992-2002) and Caux et al (journal of Experimental Medicine, 1994, vol. 180, pp. 1263-1272) and Cella et al (Journal of Experimental Medicine,

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1996, Vol. 184, pp. 747-752) all in view of de Boer (U.S. 5,874,082) and Schlom (In: Molecular foundations of Oncology, Sameule Broader, Ed, 1991, pages 95-134) with a human antibody with a human Fc region that can compete for binding with S2C6 on the CD40 receptor. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of the abstract of Bender et al on the production of human antibodies having Fc region from the fusion of human antibody fragment obtained from phage display libraries and the Fc region of a human antibody.

7. Claims 26, 38, 42, 27, 39, 37, 40, 42, 58, 59, 66, 61, 62, 79, 75 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paulie et al (Cancer Immunology, Immunotherapy, 1985, Vol. 20, pp. 23-28) and Francisco et al (The Journal of biological chemistry, 1997, Vol. 272, pp. 24165-24169) in view of deBoer (U.S. 5,874,082) and Schlom (In: Molecular foundations of Oncology, Sameule Broader, Ed, 1991, pages 95-134) .

Paulie et al teach that the S2C6 antigen is found on bladder cancer cells and on B lymphocytes.

Francisco et al teaches that the toxin bryodin fused to the sFv fragment of the G28.5 antibody which binds to CD40 is cytotoxic to a non-hodgkin's lymphoma cell line, a multiple myeloma cell line , a b-cell leukemia and a hodgkin's disease cell line. Francisco et al teach that all these cell lines express CD40. Francisco et al teach that because the single chain immunotoxin comprising bryodin was cytotoxic without the addition of a translocation domain, this is indicative that bryodin itself possesses said translocation domain (page 24169, first column, lines 3-15).

DeBoer teaches how to make humanized anti-CD40 antibodies. DeBoer does not specifically make a humanized anti-CD40 S2C6 antibody.

Schlom teaches that in all of the previous reported human trials in which non-immunosuppressed patients were treated with multiple doses of murine antibodies only the first

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and perhaps the second dose of said antibody was efficiently reaching the tumor site due to the HAMA response. Schlom teaches that it is unrealistic to assume that just one or two administrations of any anti-cancer therapeutic would be effective. Schlom teaches that the answer to this problem is the humanization of the murine antibodies (pages 97-98, bridging paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to treat B cell malignancies by the administration of a humanized S2C6 antibody conjugated or fused to bryodin, wherein the S2C6 antibody was a tetravalent full antibody or a single chain Fv fragment. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Francisco et al on the cytotoxicity of bryodin fused to anti-CD40 antibodies on B cell malignancies.

8. All other rejections and objections as stated in Paper no. 7 are withdrawn.

### *Conclusion*

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

  
Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

June 2, 2003